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EXAMINER	
GRUN, JAMES LESLIE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/898,398	Applicant(s) HUTCHISON
	Examiner James L. Grun, Ph.D.	Art Unit 1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-61 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-61 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1641.

The drawings are objected to for the reasons that the panels of Figs. 2 and 13-17 should be separately labelled, e.g. as Fig. 2A and Fig. 2B. Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Submission of corrected drawings may no longer be held in abeyance pending the indication of allowable subject matter. Failure to take corrective action within the set period will result in **ABANDONMENT** of the application. Direct any inquiries concerning drawing review to the Drawing Review Branch at (703) 305-8404.

The disclosure is objected to because of the following informalities: page 31, line 21, "week" should be --weak--; page 32, line 9, "form" should be --from--; page 32, line 27, --lysyl-- should be recited. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claims 35 and 36 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the disclosed biological materials are: (1) capable of performing any of the functions as claimed; (2) known and readily available to the public; (3) reproducible from the written description; or, (4) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809.

It is unclear if cell lines which produce antibodies having the exact chemical identity and properties of the antibodies designated PTA-3496 are known and publicly available, or can be reproducibly isolated without undue experimentation. Accordingly, filing of evidence of the reproducible production of the cell line and antibodies necessary to practice the instant invention or filing of evidence of deposit is required. Without a publicly available deposit of a cell line producing antibodies having the appropriate properties, one of skill in the art could not be assured of the ability to practice the invention. The properties of the instantly disclosed monoclonal antibody are entirely unknown so that one would not be assured of the ability to make or use this monoclonal antibody in order to function and/or perform in the invention as claimed. Exact replication of: the cell line; the cell lines which produce the chemically and functionally distinct antibodies; and/or, the

antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Therefore, it would require undue experimentation to reproduce the monoclonal antibody species chemically as produced by the hybridoma designated PTA-3496. A suitable deposit of the hybridoma may satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph, if function of the antibody in the invention is in evidence. See the criteria set forth in 37 CFR §§ 1.801-1.809.

If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty, that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent and that the biological materials will be replaced should they ever become non-viable, would satisfy the deposit requirement made herein.

If the deposits have not been made under the Budapest Treaty, then in order to certify that the deposits meet the criteria set forth in 37 CFR §§ 1.801-1.809, applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposits will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) the deposits were viable at the time of deposit; and,
(e) the deposits will be replaced if they should ever become non-viable.

Moreover, the ability of one to make and use humanized antibody is dependent upon one knowing the sequences of the appropriate complementarity determining regions of an antibody structure which functions in the invention. As it is not even clear that the disclosed monoclonal antibody functions in the invention, and the structure thereof is undisclosed, one would be unable to make and use a humanized antibody derived from this particular monoclonal antibody. Further, one would be unable to derive humanized antibodies from a polyclonal antibody population with a plurality of unknown structures. Applicant provides no written description of any structure of an antibody which functions in the invention, thus one would not know how to make or use any humanized antibodies as instantly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-26, 29-41, and 44-61 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-22, 40, and 41, the functional recitation of "whereby" does not constitute a positive limitation in any patentable sense, --wherein-- is suggested.

In claim 23, and claims dependent thereupon, "the" bioactive, three-dimensional epitope lacks antecedent basis and, in dependent claims other than claim 26, is not clear as to what sequence or portion of the hormone is encompassed within the metes and bounds of the invention.

In claim 24, and claims dependent thereupon, "the" amino terminus lacks antecedent basis and is not clear as to what sequence or portion of the hormone is encompassed within the metes and bounds of the invention.

In claim 29, and claims dependent thereupon, "the" bioactive amino-terminal portion lacks antecedent basis and, in dependent claims other than claim 31, is not clear as to what sequence or portion of the hormone is encompassed within the metes and bounds of the invention.

In claim 39-41, 44, 45, "the" bioactive three-dimensional epitope lacks antecedent basis.

In claims 44 and 45, it is not clear if the variant or fragment is that of the antibody or of the epitope.

In claim 46, and claims dependent thereupon, "the" bioactive, three-dimensional epitope lacks antecedent basis and, in dependent claims other than claim 48, is not clear as to what sequence or portion of the hormone is encompassed within the metes and bounds of the invention.

In claims 52 and 55, and claims dependent thereupon, "the" bioactive three-dimensional epitope lacks antecedent basis and is not clear as to what sequence or portion of the hormone is

encompassed within the metes and bounds of the invention. In these claims, "the" complex also lacks antecedent basis.

Claims 60 and 61 are method claims and, as such, they should clearly set forth the various method steps in a positive, sequential manner using active tense verbs such as mixing, reacting, and detecting. These claims are indefinite because without any active, positive steps delimiting how the method is actually practiced it is unclear what method/process applicant is intending to encompass. The claims should also clearly state each component used in the method and the relationship of the various components, and should not be a mere cataloging of parts. The claims should also conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim. In these claims, "the" bioactive three-dimensional amino-terminus lacks antecedent basis.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 39 and 42-43 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. There is no indication that the product(s) as claimed are isolated and no claimed degree of purity for the product(s) which would indicate "the hand of man". Thus, the products as claimed are considered a product of nature which is non-statutory subject matter.

Claims 60 and 61 are rejected under 35 U.S.C. 101 because the claimed recitation of an assay, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-15, 18, 19, 21, 23-25, 27, 29, 30, 32-35, 37, 38, 40, 42-47, 49, 50, 52-55, 58, and 60 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Kuronen et al. (Eur J. Clin Chem Clin Biochem 35(6): 435, 1997).

Kuronen et al. immunized rabbits, mice, and hens with synthetic human parathyroid hormone (parathyrin) coupled via glutaraldehyde to keyhole limpet hemocyanin in order to elicit antibodies. The reference generated monoclonal antibodies to parathyrin and isolated polyclonal antibodies binding to the hormone by affinity purification with human parathyroid hormone peptides. The antibodies were used in different combinations for assays of parathyroid hormone in samples, including the use of labelled antibodies specific for the peptide consisting of amino acid residues 1-30 of the hormone which comprises residues 1-13 (see e.g. Fig. 2).

Claims 1-4, 6-15, 23-25, 27, 29, 30, 32-35, 37, 38, 40, 42-47, 49-55, and 60 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Brown et al. (J. Immunol. Meth. 109: 139, 1988).

Brown et al. immunized sheep with a bioactive N-terminal human parathyroid hormone fragment coupled via glutaraldehyde to keyhole limpet hemocyanin in order to elicit antibodies. The reference isolated the polyclonal antibodies binding to the hormone by affinity purification, labelled the antibodies with an acridinium ester, and used the antibodies to assay hormone in samples with a sandwich immunoassay. The reference also discloses several monoclonal anti-PTH antibodies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-35, 37-50, 52-55, 58, 60, and 61 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kuronen et al. (Eur J. Clin Chem Clin Biochem 35(6): 435, 1997) in view of Gao et al. (J. Bone Min. Res. 14(Suppl. 1):S446, Abstract SU057, 1999) and John et al. (J. Clin Endo Metab. 84: 4287, 1999).

The teachings of Kuronen et al. are as set forth previously and differ from the invention as instantly claimed in not teaching C-terminal antibodies isolated with the fragment of parathyroid hormone (PTH) consisting of amino acid residues 39-84 and in not teaching the importance and use of antibodies specific for an epitope of PTH within the first N-terminal 13 amino acid residues.

Gao et al. and John et al. teach the importance of determining full length PTH in samples in which amino-terminally truncated inactive PTH(7-84) fragments may be present and teach the use of antibodies, isolated by affinity chromatography, specific for residues 39-84 and 1-6 of human PTH a sandwich immunoassay.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted antibodies isolated as specific for the fragments of PTH taught by Gao et al. and John et al. in the methods of Kuronen et al. for the benefits taught in Gao et al. and John et al. for the detection of full length PTH discriminated from the truncated inactive PTH fragment present in patient samples. One would have had an extremely reasonable expectation that antibodies specific for the fragment comprising residues 1-6 would also bind to the fragment consisting of residues 1-13 which fully encompasses the relevant epitope defined in Gao et al. and John et al. It

would have been obvious to formulate the reagents of Kuronen et al., as modified, into a kit since that is conventional for convenience, economy, and reproducibility.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 51, 56, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuronen et al. in view of Gao et al. (1999) and John et al. as applied to claims 1-35, 37-50, 52-55, 58, 60, and 61 above, and further in view of Gao et al. (Clinica Chim. Acta 245: 39, 1996).

The teachings of Kuronen et al., as modified, are as set forth above and differ from the invention as instantly claimed in not teaching acridinium ester labels for use in immunochemiluminometric assays for PTH.

Gao et al. (1996) teach acridinium ester labels for use in immunochemiluminometric assays for PTH.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted acridinium ester labels for immunochemiluminometric assay of PTH as taught by Gao et al. in the methods of Kuronen et al., as modified, because Gao et al. teach that the use of this detection system was well known in the art for the detection of PTH and one would have been motivated to substitute a known detection system with an extremely reasonable expectation of success for the benefits taught in Gao et al. such as the avoidance of radionuclide

storage and disposal and the sensitivity, easy labelling and commercial availability of acridinium ester as label.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kuronen et al. in view of Gao et al. (1999) and John et al., and further in view of Gao et al. (1996), as applied to claims 1-35, 37-58, 60, and 61 above, and further in view of Immunotopics International (Reference AF).

The teachings of Kuronen et al., as modified, are as set forth above and differ from the invention as instantly claimed in not teaching determination of PTH levels in hypoparathyroidism.

Immunotopics International teach the clinical significance of determinations of intact PTH.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have determined samples from hypoparathyroid patients in addition to those of hyperparathyroid patients with the assay of Kuronen et al., as modified, because of the well known clinical significance of such determinations taught in the Immunotopics International reference.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Adermann et al. (U.S. Pat. No. 6,030,790) teaches antibodies that bind to epitopes in N-terminal PTH fragments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (703) 308-3980. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (703) 305-3399.

The phone numbers for official facsimile transmitted communications to TC 1600, Group 1640, are (703) 872-9306, or (703) 305-3014, or (703) 308-4242. Official After Final communications, only, can be facsimile transmitted to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. The above inquiries, or requests to supply missing elements from Office communications, can also be directed to the TC 1600 Customer Service Office at phone numbers (703) 308-0197 or (703) 308-0198.

James L. Grun, Ph.D.
November 10, 2003

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641